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Research Article

Is There a Relationship Between Bupropion Plasma Levels and Blood Pressure Increase?

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Abstract: Bupropion is largely used as an antidepressant and smoking cessation therapy. The aim of this work was to evaluate effects of increased bupropion plasma levels on blood pressure and heart rate in patients with depression. A total of sixty patients with a diagnosis of depression completed this naturalistic study. Bupropion was administered in 150 mg/day dose. Bupropion plasma levels were measured on the 7^{th} and 14^{th} day of treatment. Heart rate, systolic and diastolic blood pressure were measured for each patient on the 7^{th} and 14^{th} days of treatment. The results of this study did not show any statistically significant blood pressure or heart rate changes with elevating bupropion plasma levels. No significant difference in blood pressure or heart rate was observed by reaching the therapeutic plasma levels of bupropion. Although our results did not suggest any effect of bupropion plasma levels on heart rate and blood pressure, therapeutic benefit of bupropion to treat depression in hypertensive patients should be carefully weighed.
Keywords: Blood pressure, Bupropion, Heart rate, Plasma level

INTRODUCTION

Bupropion is a selective norepinephrine and dopamine reuptake inhibitor without any significant effects on the serotonergic system [1]. Bupropion has been available for the treatment of psychiatric diseases since 1989 and has been approved both as an antidepressant and as a non-nicotine aid to smoking cessation [2, 3]. Bupropion XL has a half-life of 21 hours and plasma concentrations become stable after 5-7 days of drug use which has increased its tolerability [4]. Once-daily bupropion XL is bioequivalent to both twice-daily bupropion SRand thrice-daily bupropion as evidenced by similar peak plasma concentrations (Cmax), area under the curve (AUC), and plasma concentration versus time profiles [2].

In comparison with the serotonergic drugs, bupropion is less associated with certain side-effects such as weight gain, somnolence and sexual dysfunction which results in its being more prescribed. The most common side-effects of bupropion is dry mouth, nausea, constipation, headache and insomnia [1]. However rather rare but important adverse events such as high blood pressure, seizures, allergic reactions and hallucinations have also been reported [3]. Norepinehrine reuptake inhibition property of bupropion is found to be related with hypertension and this relation has been reported in other drugs with noradrenergic properties such as venlafaxine [5] and reboxetine [6].

In an earlier placebo-controlled study, patients received bupropion SR in doses ranging from 150mg/day mg to 400 mg/day for 8 weeks without any significant effects on blood pressure [7]. In a study where bupropion SR was tested for smoking cessation, there was a statistically non-significant trend toward a greater incidence of treatment-emergent hypertension in those patients that received bupropion combined with a nicotine patch in comparison with placebo or bupropion alone [8]. Tonstad *et al*. studied the efficacy and cardiovascular side-effects of bupropion SR in a 7-week treatment regimen for smoking cessation in smokers with cardiovascular disease, and they did not report any clinically significant changes in blood pressure [9]. There have been various studies questioning the relationship between bupropion and increased blood pressure with conflicting results.

The aim of this study was to evaluate the relationship between serum bupropion levels and arterial blood pressure (BP) and heart rate.

MATERIAL AND METHODS

In this study we evaluated patients who were on 150 mg/d oral bupropion treatment with a diagnosis of major depressive disorder between November 2011 to May 2013 at psychiatry department of Uskudar University Neuropsychiatry Istanbul Hospital. Uskudar University Institutional Review Board approved the study protocol. Patients were excluded if their BMI was >28 kg/m^2, if they were taking any antihypertensive drugs or medications known to affect plasma levels of

bupropion or blood pressure. Informed consent was obtained from all participants.

Resting blood pressure measures of all subjects were evaluated in the morning, between 8:00 AM and 9:00 AM, after an overnight fast. Arterial blood systolic and diastolic pressures and heartrate were measured after 10 min of supine rest, by trained nurses using a standard mercury sphygmomanometer (Heine) with a cuff size appropriate to individual. Measurements were taken daily for 14 days for every patient, andthe results were averaged to get values of first week and second week mean diastolic and systolic blood pressures. BMI was also calculated by taking a person's weight and dividing by their height squared.

Blood sampling

Plasma bupropion levels were measured on the 7th and 14th day of treatment. To measure the bupropion plasma levels venous blood samples are collected from the patients 12 hours after the last drug dose.Approximately 3-5 mL of venous blood was collected from each patient into EDTA Vacutainer tubes. The blood samples were processed immediately by centrifugation. The samples were stored at -20 °C before frozen shipment on dry ice for High Performance Liquid chromatography with Tandem Mass Spectrometry (HPLC/MS) analysis.

Statistical analysis

The results are expressed as means±standart deviation. Statistical analysis of the data was performed using the SPSS 16 program package. The results were analyzed using analysis of variance, Student's t-test analysis. The level of significance was taken as $p<0.05$.

RESULTS

There were a total of 60 patients (male: 27, 45%, female: 33, 55%). Mean age of the patients were 57.9 years. Mean bupropion plasma levels at the end of the first and second weeks were 26.65 ng/ml and 31.23 ng/ml respectively. Mean systolic BP at the end of the first and second weeks were 119 mmHg and 121,6 mmHg respectively. Mean diastolic BP at the end of the first and second weeks were 74.43 mmHg and 75.17 mmHg respectively. Mean heart rate measurements at the end of the first and second weeks were 83.8 beats/minute and 86.3 beats/minute. Mean BMI was 27.7. Mean systolic BP, diastolic BP, heart rate and bupropion plasma levels are presented on Table 1.

Table 1: Mean systolic BP, diastolic BP, heart rate and bupropion plasma levels

	7th day	**14th day**	**p**
Systolic BP (mmHg)	119,56±7,4	121.27± 13	0,079
Diastolic BP (mmHg)	74.43±8.7	75.17±7	0,456
Heart rate (pulse/min)	83.8±10	86.3±10	0,035
Bupropion plasma level (ng/ml)	26.6±22.8	131.226,6±61,8	p<0.05

Paired samples correlation test was applied for the differences between the mean systolic BP values, diastolic BP values, and mean heart rates values of the first and second week. The difference between the two weeks was not statistically significant for systolic BP, diastolic BP and mean heart rates ($p>0.05$).

DISCUSSION

Drug-induced blood pressure elevations represent an important and modifiable cause of secondary hypertension. Patients with preexisting hypertension may develop a worsening of blood pressure control when these drugs are initiated. The mechanism of action of bupropion on blood pressure and heart rate are still unknown [10]. The effectiveness and safety of bupropion have been demonstrated in many studies; however, its pharmacological profile, dosage and administration, clinical effectiveness, safety and tolerability are still a matter of discussion [11]. Some of the cardiovascular side effects of bupropion include orthostatic hypotension and the exacerbation of hypertension [12] and chest pain [13,14].

Patterson and Herity also reported a case of myocardial infarction that thought to be related with bupropion use [15]. Paganelli *et al*. investigated the effects of bupropion on hemodynamic parameters in pentobarbital-anesthetized mongrel dogs and reported that bupropion can elevate the pulmonary pressure[16].

This is the first study evaluating relationship of the blood pressure and heart rate changes with the bupropion plasma levels. The results of this study did not show any statistically significant blood pressure or heart rate changes with elevating bupropion plasma levels. We found that increased plasma bupropion levels by the end of the second week of treatment was associated with 1,7 mmHg increase in mean systolic BP and 0,74 mmHg increase in mean diastolic BP, however these findings were not statistically significant.

Although there have been spontaneous reports of hypertension in clinical practice, bupropion alone has not been associated with effects on blood pressure relative to placebo in clinical trials [17]. However, in a study in which bupropion was combined with a nicotine patch, there was an increased incidence of treatment-emergent hypertension in the combination group compared to the placebo group or the bupropion alone group, and the researchers suggested that blood pressure should be monitored in patients receiving bupropion in combination with a nicotine patch [2]. We did not found a statistically significant increase in mean heart rate measurements.

We have measured bupropion plasma levels on the 7th and 14th days. Bupropion-XL reaches plasma steady-state by the 8th day therefore we have not considered further drug monitoring beyond the 14^{th} day. Bupropion-XL is extensively metabolized via cytochrome P450 (CYP) 2B6 to its active metabolites with some contribution of the other CYP isoenzymes such as 2A6, 2C9, 2D6, 2E1 and 3A4 [17]. Bupropion has 3 metabolites: hydroxybupropion, threohydrobupropion, and erythrohydrobupropion [18]. Hyroxybupropion is the major active metabolite of bupropion, which is reported to have similar potency to bupropion. At steady state Cmax of bupropion-OH is 4-7 times higher than bupropion [19]. The major limitation of the study is that, we measured plasma levels of total bupropion; therefore the measurements included do not reflect the levels of metabolites. If bupropion metabolites had been measured than our results might have been interpreted differently. Another limitation is the lack of information about the genetic profiles of patients in terms of CYP2B6 activity, which might as well have affected drug plasma levels in some of our patients.

Although there have been spontaneous reports of hypertension in clinical practice, bupropion alone has not been associated with effects on blood pressure relative to placebo in clinical trials [20]. There is a probability plasma level dependent effect on blood pressure, but in this study we could not find any statistically significant difference in blood pressure and heart rate measures of the groups. The mean body mass index was 27.7 in study group. Although this value cannot be considered as obesity, it represents “overweight” which is a major risk factor for hypertension [21].

CONCLUSION

No significant difference in blood pressure or heart rate was observed by reaching the therapeutic plasma levels of bupropion. Although our results did not suggest any effect of bupropion plasma levels on heart rate and blood pressure, therapeutic benefit of bupropion to treat depression in hypertensive patients should be carefully weighed.

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